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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,383	12/22/2000	Peter Van Vlasselaer	4750-0001.30	9470

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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,383	VLASSELAER ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/17/2004 has been entered. An action on the RCE follows.

2. Claim 15 has been cancelled. New claim 24 has been added. Therefore, Claims are 16-24 are pending.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

4. Applicants submission of a declaration under 37 C.F. R. 1.132 is acknowledged

Claim Rejections - 35 USC § 103, maintained

5. The rejection of claims 15-23 under 35 U.S.C. 103(a) as being unpatentable over Huland et al. (U. S. Patent No. 5,780,012) in view of both Debs et al. (J.of Imm. Vol. 140: 3482-3488) and Ruskewicz et al. (U. S. Patent No. 5,971,951) further as evidenced by (Nayar et al., U.S. Patent No: 5, 874, 408 or Hora et al., U.S. Patent No: 5, 078, 997) is maintained. Applicants has cancelled claim 15 and added claim 24. Therefore, the pending rejections are applicable to claims 16-24.

Applicants' arguments and remarks filed 5/17/04 have been fully considered but are not deemed to be persuasive for reasons set forth in the Office Actions of 1/13/03, 11/17/03 and further argued below. Applicants assert that Huland et al. reference does not teach an aerosol compositions having a known gamma-IFN biological activity and comprising a stabilizing agent consisting of sugar, alcohol, amino acid, or combination thereof. In addition, it is asserted that the reference does not teach that the aerosol has a gamma-IFN biological activity substantially the same as that of the solution. This is not found to be persuasive because Huland et al. reference clearly recites these limitations. Huland et al. teach that the aerosol composition contains salt, buffer or sugar (column 5, lines 45- 47). It also teaches that the composition may contain amino acids (column 5, lines 55- 57) and alcohol such as polyethyleneglycol (column 6, lines 1- 3). Huland et al. also teach the inclusion of cytokines in the aerosol composition including interferon gamma (column 4, lines 45- 55). In addition, the Debs et al. reference teaches the use of aerosolized IFN-gamma to stimulate alveolar macrophage and blood monocyte function (abstract). It also discusses that IFN-gamma activates macrophages to release IL-1, express class II HLA (Ia) surface Ag, and lyse tumor cells. Therefore, clearly demonstrating that the IFN-gamma biological activity in the aerosol composition is substantially the same as that of the solution. In addition, Debs et al. provide an analysis of rHuTNF- α recovered as a condensate after aerosolization demonstrated that it retained full biological activity, as indicated both by migration non-denaturing gels (page 3487, 3rd paragraph). Therefore, absent evidence to the contrary it assumed that

the cytokine activity of the aerosol compositions is substantially the same as that of solution. Further, it should be noted that, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants also contend that Huland et al. teach aerosol compositions with serum protein to optimize biological effect of the cytokine. Although, the Office acknowledged this fact in the Office Action mailed on 11/17/2003, it is also true that Huland et al. describe aerosol compositions comprising one cytokine and a pharmaceutically acceptable carrier, which is an aqueous solution of a salt, buffer or sugar (column 4, lines 31-36). Aerosol composition without serum albumin but with salts to stabilize is also taught in claim 1 of Huland et al. Further, Applicants argue that the addition of salt, buffer, amino acid and sugar in Huland et al.'s aerosol compositions is not for stability purpose. Although, Huland et al. explicitly did not recite that the addition of sugar, salt and buffer to the composition provides stability of the protein, it is an inherent property of these compounds to confer stability to a native protein in the composition. The Examiner also notes the decision in *Swinehart and Sfiligoj*, 169 USPQ 226, in which it was found that mere recitation of a newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art. Although the prior art did not necessarily appreciate the mechanism or describe the stability conferred by the salts, sugar and buffer on the cytokine it is an inherent property of these compounds in the composition.

Applicant further submit a declaration and argue that gamma-IFN was known to be active in a non-covalent dimeric form, but not in its monomeric form, and it was believed that aerosolization may lead to loss of activity by creating shear conditions that result in the conversion of gamma-IFN to the inactive monomeric form. However, as indicated in the Office Action of 11/17/2003 (page 4, last paragraph) the claims of the instant invention do not recite these limitations in the claim. In addition, with respect to Applicants assertion that the claims recite novel, non obvious compositions for conferring stability to gamma-IFN solution and that previously serum albumin was commonly used as a stabilizing agent is not found to be persuasive. The following evidentiary art describe serum free stabilized proteins (Nayar et al., U.S. Patent No: 5, 874, 408) and pharmaceutical composition for IL-2 containing physiologically compatible stabilizers (Hora et al., U.S. Patent No: 5, 078, 997) that were available prior to the filing of the instant invention which recite compositions having sugar, amino acid, alcohol or a combination thereof as a stabilizing agent. Thus the claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary. Therefore, the rejection of claims 16-24 under 35 U.S.C. 103(a) as being unpatentable over Huland et al. (U. S. Patent No. 5,780,012) in view of both Debs et al. (J.of Imm. Vol. 140: 3482-3488) and Ruskewicz et al. (U. S. Patent No. 5,971,951) further as evidenced by (Nayar et al., U.S. Patent No: 5, 874, 408 or Hora et al., U.S. Patent No: 5, 078, 997) is maintained.

New Claim Rejections - 35 USC § 103

6. The rejection of claims 16-24 under 35 U.S.C. 103(a) as being unpatentable over Huland et al.(U. S. Patent No. 5,780,012) and Jaffe et al. (J. Cli. Int., 1991, Vol. 88: 297-302) in view of both Debs et al. (J. of Imm., 1988, Vol.140: 3482-3488) and Ruskewicz et al. (U. S. Patent No. 5,971,951) further as evidenced by (Nayar et al., U.S. Patent No: 5, 874, 408 or Hora et al., U.S. Patent No: 5, 078, 997).

Huland et al. teaches various aerosol compositions containing cytokines for reducing lung afflictions. The reference teaches various examples in which cytokines have been combined with mannitol and polysorbate like polysorbate 80 (see example 5). Although the specific example teaches that the composition contains 5 mg of mannitol, the specification also recites that the mannitol concentration could be 0.001 mg/ml to about 0.020 g/ml that includes the limitation of claim 18 (column 5, lines 55-60). In addition, the reference also teaches that the composition contains detergents as dispersing agents. These agents including polysorbate are present in a concentration of about 0.01mg/ml to about 0.5 mg/ml that includes the limitation of claim 20 (column 5, line 60-column 6, line 5). The composition contains about one million units of cytokines (column 6, lines 41-43). The composition containing mannitol and polysorbate in the above mentioned concentrations would have comparable viscosity to that of claim 21 and be capable of being aerosolized. This is because the viscosity of a compound at a given temperature is proportional to the radius of the capillary. Although Huland et al. describe cytokine IL-2 extensively, they also describe

interferon gamma (column 4, lines 53-54). However, the reference does not expressly discuss the volume diameter of the droplets used in the delivery.

Jaffe et al. teaches rIFN - γ formulated in an excipient composed of sodium succinate, mannitol, and polysorbate 20 (page 298). This confers stability to the composition as evidenced by as evidenced by Nayar et al. and Hora et al. without including serum albumin in the composition. rIFN - γ has a specific activity of 2.7×10^7 U/mg (page 298). Further the aerosol droplets were in the size range of 0.2-3 μm allowing for deposition in the lower respiratory tract.

The Debs et al. reference teaches the use of aerosolized IFN-gamma to stimulate alveolar macrophage and blood monocyte function (abstract). It also discusses that IFN-gamma activates macrophages to release IL-1, express class II HLA (Ia) surface Ag, and lyse tumor cells. Although the reference does not expressly discuss the stimulation of HLA-DR antigen expression, stimulation of HLA-DR antigen expression is an inherent property of IFN-gamma as indicated by Weller et al. (1993).

Ruskewicz et al. is relied upon to describe the aerosol extrusion mechanism. It teaches that when the formulation is forced through the flexible porous membrane it will form an aerosol preferably having a particle size in the range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns (column 17, lines 57-60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a composition containing mannitol and polysorbate with a specific viscosity, as described by Huland et al., because Jaffe

et al and Debs et al. teach that the aerosolized stable IFN-gamma can be delivered to respiratory tract and is capable of stimulating HLA-DR antigen expression; Ruskewicz et al. teaches the aerosol extrusion mechanism. One of ordinary skill in the art would have been motivated to use aerosolized IFN-gamma generated by forcing the composition thru defined–size openings to deliver to the respiratory tract specifically to stimulate HLA-DR antigen expression. Thus the claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary. Therefore, the instant invention is obvious over Huland et al. (U. S. Patent No. 5,780,012) and Jaffe et al. (J. Cli. Int., 1991, Vol. 88: 297-302) in view of Debs et al. (J.of Imm. Vol. 140: 3482-3488) and Ruskewicz et al. (U. S. Patent No. 5,971,951) further as evidenced by (Nayar et al., U.S. Patent No: 5, 874, 408 or Hora et al., U.S. Patent No: 5, 078, 997).

Claim Rejections - 35 USC § 112, maintained

7.The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7a. The rejection of claim 15 is under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) is maintained and applied to claims 22 and 24. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Although, the specification describes

stabilizing agents such as sugar, alcohol and amino acids it does not describes the combination of these agents (see specification page: 7, lines 26-28). Furthermore, Applicant has not explicitly recited in the specification or the originally filed claims that the composition does not include serum bovine albumin. Therefore, it appears that the instant invention was not in Applicants possession. This is a new matter rejection.

Contrary to Applicants assertion that the claim (previous claim 15 or 24) merely rephrases the passage and does not constitute new matter, the Office notes "Under certain circumstances, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention. See, e.g., *PIN /NIP,Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1248, 64 USPQ2d 1344, 1353 (Fed. Cir.2002) (Claim for a method of inhibiting sprout growth on tubers by treating them with spaced, sequential application of two chemicals was held invalid for lack of adequate written description where the specification indicated that invention was a method of applying a "composition," or mixture, of the two chemicals.)."

8. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30. If attempts to reach the examiner by telephone are unsuccessful, the

examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 10/04

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